Extending sleep to confirm insufficient sleep syndrome is challenging

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Abstract: Insufficient sleep syndrome (ISS) is prevalent, but poorly studied. This descriptive study was performed to determine its diagnostic challenges and clinical characteristics in a large (n = 3,461) retrospective sample from a single sleep laboratory. Based on actigraphy, polysomnography and multiple sleep latency tests, we diagnosed "suspected insufficient sleep syndrome" in patients with chronic sleepiness, short time in bed, longer sleep duration during weekends or vacation, and without evidence of other causes of sleepiness. For the diagnosis of "definite insufficient sleep syndrome", we additionally required objectively confirmed resolution of sleepiness with actigraphy-documented extension of time in bed. We diagnosed "suspected insufficient sleep syndrome" in 300 subjects. In 94 subjects, extension of sleep time with consecutive relief of sleepiness was attempted, but only 37 subjects succeeded, often despite being offered several attempts. "Definite insufficient sleep syndrome" was confirmed in 36 patients. In these subjects, mean time in bed after sleep extension was above 8 hr per night and 84 min longer than at baseline. Narcolepsy-like findings were frequently observed before sleep extension, but no sleep onset rapid eye movement sleep on polysomnography. This study indicates that fulfilling the diagnostic criteria of ISS is challenging in clinical practice. It further corroborates the importance of actigraphy and polysomnography for correct diagnosis.

DOI: https://doi.org/10.1111/jsr.13109

Zurich, May 13, 2020

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All authors have seen and approved the manuscript.

No co-author has received financial support for this work.

No author declares a conflict of interest defined as any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated.

Number of tables	1
Number of figures	1
Word count (summary, keywords, main body)	2000
References	15

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Summary

Insufficient sleep syndrome is prevalent, but poorly studied. This descriptive study was performed to determine its diagnostic challenges and clinical characteristics in a large (n=3461) retrospective sample from a single sleep laboratory. Based on actigraphy, polysomnography and multiple sleep latency tests, we diagnosed “suspected insufficient sleep syndrome” in patients with chronic sleepiness, short time in bed, longer sleep duration during weekends or vacation, and without evidence of other causes of sleepiness. For the diagnosis of “definite insufficient sleep syndrome”, we additionally required objectively confirmed resolution of sleepiness with actigraphy-documented extension of time in bed. We diagnosed “suspected insufficient sleep syndrome” in 300 subjects. In 94 subjects, extension of sleep time with consecutive relief of sleepiness.was attempted, but only 37 subjects succeeded, often despite being offered several attempts. “Definite insufficient sleep syndrome” was confirmed in 36 patients. In these subjects, mean time in bed after sleep extension was above 8 hours per night and 84 min longer than at baseline. Narcolepsy-like findings were frequently observed before sleep extension, but no sleep onset rapid eye movement sleep on polysomnography. This study indicates that fulfilling the diagnostic criteria of ISS is challenging in clinical practice. It further corroborates the importance of actigraphy and polysomnography for correct diagnosis.

Keywords: chronic sleep restriction, hypersomnia, alertness, excessive daytime sleepiness, differential diagnosis, wakefulness

Introduction

Insufficient sleep syndrome (ISS) occurs when a person chronically fails to obtain the amount of sleep required to maintain normal alertness and wakefulness (AASM, 2014). Recent evidence suggests that the prevalence of ISS in a sample of 989 US American college students is 10% (Williams, 2020). Using a cluster sampling procedure in 1285 high-school students who completed web-based questionnaires, a Norvegian study estimated that ISS occurs in 10.4% (Pallesen, 2011). In 181 young in-lab patients under 20 years, a Japanese team estimated the frequency of ISS even higher, i.e. 31% (Kohyama, 2018). The impact of ISS on health and performance is significant. For instance, ISS is related to metabolic disease such as diabetes, or to neurodegeneration such as Alzheimer disease (Chattu, 2019; Irwin, 2019). It enhances erroneous and risky decisions, and is linked to poorer academic performance and higher risk of accidents (van Dongen, 2003; Maric, 2018; Komada, 2008; Lee, 2015). Thus, despite its appearance as a seemingly harmless entity in otherwise healthy subjects, ISS must be regarded as a major hazard to health, well-being and prosperity in today's 24-hour society.

For diagnosing ISS, the third edition of the International Classification of Sleep Disorders (ICSD-3) requires (1) excessive daytime sleepiness (EDS) for at least 3 months, (2) a sleep time – assessed by history, with sleep logs or actigraphy – which is usually shorter than expected for age, (3) curtailment of sleep e.g. by an alarm clock or an awakening person, and longer sleep when such measures are not used, e.g. during weekends or vacations, (4) a resolution of EDS with extension of sleep time, and (5) presence of no other conditions potentially causing EDS (AASM, 2014).

Although these criteria make sense from a conceptual point of view, we experience that they are difficult to apply in a clinical setting. It is hard to define the required sleep time for a specific patient, as physiological sleep need varies greatly among individuals and seasons. In addition, it remains unclear how extensive the difference in sleep times between working and holidays should be to qualify for ISS, and how to most reliably measure it. Last, although the resolution of EDS with sleep extension appears best for verifying this diagnosis, we do not know how

much an individual patient should extend daily sleep time, and how remission of EDS should be confirmed.

The goals of this descriptive study were (a) to evaluate the diagnostic procedure of confirming ISS by applying sleep extension, and (b) to characterize patients with confirmed ISS.

Methods

In this retrospective single-center study which was approved by the local ethical committee, we re-evaluated all files of patients who were examined in-lab between 2002 and 2019 for accuracy of diagnosis along the current ICSD-3 criteria (AASM, 2014). All patients with suspected central disorders of hypersomnolence including ISS underwent 2-week actigraphy, polysomnography (PSG), and multiple sleep latency test (MSLT). Those who successfully increased mean sleep time by at least 30 minutes per 24 hours over 2 weeks, confirmed by actigraphy, with consecutive remission of EDS, confirmed by MSLT or maintenance of wakefulness test (MWT), were considered “definite ISS” patients. In the other patients who fulfilled all other ICSD-3 diagnostic criteria except recorded EDS remission after sleep extension, we diagnosed “suspected ISS”. The reason for not having performed sleep extension in those patients were either lack of feasibility or motivation of the patients or of the doctors, given the time-consuming and expensive follow-up examinations. Patients on psychoactive drugs or with any condition potentially causing EDS were not included in this analysis. To avoid an impact of major chronobiological misalignment, we excluded shift workers.

As this study spans over 17 years, we used different types of actimeters, i.e. Actiwatch AW4, AW Light, AW7 (Neurotechnology), Actiwatch AW2, Actiwatch Spectra (Philips), and related software, i.e. Sleep Analysis versions 1 to 7, Actiware versions 5 to 7. However, ‘time in bed’ at night (TIB, ‘time asleep’) was based on bedtimes which were determined in a semiautomatic way (software, sleep log information, visual inspection of activity profiles and light info) and is

therefore comparable between all systems, as recordings were always supervised by the same authoring team. Immediately after 2 weeks actigraphy, we performed and scored overnight video-PSG as described before (Imbach, 2015). To assess EDS, PSG was followed by MSLT (4–5 sleep opportunities every 2 hours) (Littner, 2005). After sleep extension counselling to a subset of patients, 2 weeks actigraphy was again performed prior to MSLT or MWT (4x40 minutes to assess the ability to stay awake in soporific conditions during daytime), but without another PSG (Littner, 2005). Statistical analyses were performed with SPSS 22.0, and included the assessments of means and standard deviations, and of median values in samples with extreme outliers.

Results

Among the included 3461 patients, ISS was considered in 337 subjects (Figure 1). In 94 subjects (28% of 337 subjects), actigraphy-documented extension of sleep time and subsequent relief of EDS as measured by MSLT/MWT was attempted, but only 37 (39% of 94 subjects) subjects finally managed to extend their average sleeping time at least 30 minutes per night. Of these, one HLA-DQB1*0602-positive patient was finally diagnosed with narcolepsy type 2, as he extended habitual sleeping times by more than 90 minutes, but without relief of EDS or of increased rapid eye movement (REM) sleep pressure. In the other subjects, EDS remitted as documented by MSLT/MWT. These 36 subjects (1.0% of the entire cohort) were finally diagnosed with “definite ISS”, and 300 patients (8.7%) with “suspected ISS”. Sex, age, Epworth sleepiness scale, history of sleep attacks, reported sleep duration per 24 hours and referring reasons were similar in both groups.

Detailed characteristics of the 36 “definite ISS” subjects are summarized in Table 1. The most common referring reasons to our sleep unit were “sleepiness of unknown origin” (n=17), recurrent sleep attacks (n=7), suspected narcolepsy (n=6), suspected sleep apnea (n=3), and suspected idiopathic hypersomnia (n=2). Only one subject was referred because ISS was

suspected. Eleven subjects (31%) worked in jobs such as taxi or truck driver, i.e. professions which are directly dependent on fitness to drive.

Baseline actigraphy revealed a mean TIB during the main sleeping period over all recorded nights of 6 hours 48 minutes, and the mean difference between working days and weekends/holidays was 1 hour 37 minutes. On MSLT, all patients had pathologically low mean sleep latencies (average: 4.0±1.4 minutes), and 15 patients (42%) had multiple (≥2) sleep onset REM periods, i.e. REM sleep that occurred within 15 minutes after sleep onset, whereof 19% displayed the sleep stage sequence "wakefulness→NREM1→REM".

To resolve EDS, 15 patients (42% of 36 subjects) succeeded with one actigraphy-recorded attempt, 14 patients (39%) needed 2 attempts, 3 patients (8%) 3 attempts, and 4 patients (11%) performed actigraphy and MSLT/MWT recordings 4 times until objective EDS remitted. The reason for unsuccessful attempts was always absent or insufficient sleep extension. On actigraphy, mean TIB was 1 hour 24 minutes longer than before extension ($p=0.004$). The mean difference between working days and weekends/holidays was reduced by only 12 minutes ($p=0.09$). On MSLT ($n=25$), averaged mean sleep latency was 12.2±2.8 minutes ($p<0.001$), and multiple sleep onset REM periods were no longer observed. In the 3 single REM-containing naps, we found the sequence "wakefulness→NREM1→NREM2→REM".

Discussion

This study shows that proving ISS by applying sleep extension is tough and expensive: only 39% of 94 patients who were carefully informed and accompanied by our sleep team during sleep extension were able to execute a proper sleep extension, and most of them succeeded only because we offered multiple attempts. Thus, 61% of patients failed, again many of them despite having being offered more than one attempt to extend time in bed. We suspect that extending TIB could not be completed over a longer period of time because environmental, occupational, and family factors made it impossible, or because motivation for curtailing waking

time was insufficient. It is enlightening that 11 of the 36 successful patients were working in jobs which legally require unrestricted vigilance.

Therefore, with current sleep laboratory standards, it seems difficult to solidly diagnose ISS. This difficulty is further gravened by the fact that actigraphy – the only currently available method to objectively measure rest-activity and sleep-wake rhythms – is not reimbursed in many countries, and many sleep centers only perform 1-week actigraphy recordings which may not be sufficient.

In 36 patients with “definite ISS”, PSG revealed high sleep efficiency and low mean sleep latency, but a REM sleep latency below 15 minutes did not occur. Mean sleep latencies on MSLT were often in the typical range of narcolepsy patients, and 42% of patients had multiple sleep onset REM periods, a critical element for the diagnosis of narcolepsy type 1 and 2 (AASM, 2014). Seven patients revealed the sleep stage sequence NREM1 directly followed by REM sleep, which may be indicative of narcolepsy (Marti, 2009). These results suggest that MSLT alone is not sufficient to distinguish ISS from other forms of hypersomnia

Patients with “definite ISS” slept less than 7 hours per night on average, but the interindividual variation in sleep duration was considerable. After sleep extension with remission of EDS, mean sleep duration was more than 8 hours per night, indicating that 7 or 7½ hours sleep may not be sufficient for many of us, which is in agreement with basic sleep studies in humans (van Dongen, 2003; Klerman, 2008). The difference of sleep duration between working days and weekends/holidays was similar at baseline and after successful sleep extension.

Altogether, future revised diagnostic criteria may consider that this difference might not be specific enough for ISS. On the other hand, only REM sleep latency below 15 minutes on PSG might specifically discriminate narcolepsy from ISS, whereas classical MSLT findings appear unspecific (Andlauer, 2013). Last not least, diagnostic sleep extension appears a valid concept, but this study indicates that a large portion of patients fails to fulfill it. The clinical

introduction of novel unobtrusive devices for measuring EEG, sleep and sleep-wake rhythms in a home setting might contribute to finding optimized diagnostic criteria.

Although it builds on a long-time experienced team and on solid objective outcome parameters, this retrospective study has limitations: we probably missed many ISS patients because their sleep was too short every night, without a difference between working days and weekends, as for instance in young parents whose children wake up irrespective of the day. These subjects were not included as they did not fulfil all diagnostic criteria for ISS. In addition, less than 30% of ISS patients were followed by sleep extension, which constitutes an inclusion bias, although there was no systematic procedure to select subjects for sleep extension, apart from a higher motivation of subjects with a profession which is dependent on proven normal vigilance.

Acknowledgements

None.

Disclosures

Authorship: All authors listed on the manuscript have contributed significantly to the collection, analysis and/or interpretation of the data. All authors have read and approved the submitted version.

Conflict of interest:

Financial arrangements or connections that are pertinent to the submitted manuscript: None for any author.

Non-financial interests that could be relevant to the submitted manuscript: None for any author.

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Table 1. Actigraphy, polysomnography, Multiple Sleep Latency Test and Maintenance of Wakefulness Test results of the 36 "definite ISS" subjects. Data are given as means ± standard deviations, or as numbers and percentages of the "definite ISS" population.

	Baseline	**Final Follow-Up**
Demographic data		
Mean age in years	**35.4**±10.6 (18-66)	
Female gender	**14** (37%)	
Questionnaires and history		
Epworth sleepiness scale	**12.2**±4.6 (4-21)	**6.9**±3.7 (1-16)
Fatigue severity scale	**4.5**±1.4 (1.7-6.5)	**3.1**±1.8 (1.3-5.8)
Sleep attacks	**17** (47%)	**0** (0%)
Actigraphy		
'Time in bed': all nights	**6h48**±0h48 (5h17-8h25)	**8h12**±0h55 (6h35-9h53)
'Time in bed': working days	**6h19**±0h47 (4h55-7h57)	**7h38**±0h55 (5h37-9h05)
'Time in bed': weekends/holidays	**7h54**±1h18 (5h35-11h22)	**8h58**±1h11 (6h48-11h12)
Difference working days-weekends	**1h37**±1h05 (0h0-4h18)	**1h25**±1h19 (0h12-5h35)
Daytime naps	**9** (25%)	**1** (3%)
Polysomnography		
% Non-Rapid Eye Movement (NREM) 1	**7.8**±5.4 (1.0-26.4)	
% NREM 2	**49.5**±8.2 (28.0-62.8)	
% NREM 3	**18.5**±7.2 (4.2-33.3)	
% REM	**19.9**±5.9 (3.0-32.4)	
Sleep efficiency (%)	**95.0**±8.1 (55.4-99.8)	
Sleep latency to NREM 2 (minutes)	**13.0**±7.5 (2.0-30.5)	
Sleep latency NREM to REM (minutes)	**84.0**±41.6 (37.5-189.0)	
Arousal index	**8.4**±5.0 (0.0-20.8)	
Periodic limb movement d. sleep index	**1.4**±5.3 (0.0-31.0)	
Apnea-hypopnea index	**3.5**±4.4 (0.0-11.8)	
Multiple Sleep Latency Test	n=36	n=25
Mean sleep latency (minutes)	**4.0**±1.4 (1.5-7.0)	**12**.2±2.8 (10.0-20.0)
≥2 sleep onset REM periods (patients)	**15** (42%)	**0** (0%)
NREM 1→REM sequence (patients)	**7** (19%)	**0** (0%)
NREM 1→REM sequence (no. of naps)	**10**/**44** (23%)	**0**/**3** (0%)
Maintenance of Wakefulness Test		n=11
Mean sleep latency (minutes)		**38.8**±1.9 (34.9-40.0)

Figure 1. Flowchart indicating patient inclusion, diagnostic procedures and final diagnoses. ISS: insufficient sleep syndrome.